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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/787,421	02/26/2004	Majed M. Hamawy	960296.99187	5432

27114 7590 12/19/2008

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EXAMINER	
ROONEY, NORA MAUREEN	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
12/19/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

pat-dept@quarles.com

Office Action Summary	Application No.	Applicant(s)	
	10/787,421	HAMAWY, MAJED M.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-16,18 and 19* is/are pending in the application.

4a) Of the above claim(s) *14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed on 09/29/2008 is acknowledged.

2. Newly added claims 18-19 and pending and under consideration as they read on a method for monitoring whether an animal is experiencing kidney transplant rejection by detecting the protein of SEQ ID NO: 1 in a kidney tissue sample.

3. Claims 14-16 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 10/02/2006.

4. The following rejections are necessitated by the amendment filed on 09/29/2008.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: a method of monitoring whether a human that has received a transplanted kidney is experiencing kidney transplant rejection, the method comprising: analyzing a sample of the kidney of the human for the presence of a marker protein selected from the group consisting of: (a) phosphorylated protein which is SEQ ID NO: 1 in a form comprising phosphorylated tyrosine wherein the analyzing comprises: contacting the

sample or a homogenate thereof with a labeled antibody that specifically binds to SEQ ID NO:1 and an anti-phosphotyrosine antibody; and (b) protein which is SEQ: ID NO. 1; wherein the analyzing comprises: contacting the sample or a homogenate thereof with a labeled antibody that specifically binds to SEQ ID NO: 1; detecting the extent to which labeled antibody becomes bound to the marker protein or said fragment of the phosphorylated marker protein as a result thereof; and either: (i) comparing the amount of marker protein bound to the labeled antibody to a known standard to diagnose whether the human is experiencing kidney transplant rejection, whereby the method is conducted such that if no such marker protein is thereby detected in the sample, or if the amount of marker protein thereby detected in the sample is below a known standard level, such a result would be indicative of kidney transplant rejection; or (ii) comparing the amount of said fragment of the phosphorylated marker protein bound to the labeled antibody to a known standard to diagnose whether the human is experiencing kidney transplant rejection, whereby the method is conducted such that if no such fragment of the phosphorylated marker protein bound to the labeled antibody is thereby detected, or if the amount of such fragment of the phosphorylated marker protein bound to the labeled antibody thereby detected is below a known standard level, such a result would be indicative of kidney transplant rejection; does not reasonably provide enablement for: a method of monitoring whether a human that has received a transplanted kidney is experiencing kidney transplant rejection, the method comprising: analyzing a sample of the kidney of the human for the presence of a marker protein that is selected from the group consisting of: (a) phosphorylated protein which is SEQ. ID NO. 1 in a form comprising phosphorylated tyrosine; and (b) protein which is SEQ ID NO:1 wherein the analyzing comprises: contacting the sample with **a labeled**

antibody that specifically binds to said marker protein; detecting the extent to which **the labeled antibody** becomes bound to the marker protein as a result thereof; and comparing the amount of marker protein bound to the **labeled antibody** to a known standard to diagnose whether the human is experiencing kidney transplant rejection, whereby the method is conducted such that if no such marker protein is thereby detected in the sample, or if the amount of marker protein thereby detected in the sample is below a known standard level, such a result would be indicative of kidney transplant rejection of claim 18; and a method of monitoring whether a human that has received a transplanted kidney is experiencing kidney transplant rejection, the method comprising: analyzing a sample of the kidney of the human for the presence of **a marker protein that is phosphorylated protein which is SEQ ID NO: 1 in a form comprising phosphorylated tyrosine**; wherein the analyzing comprises contacting a homogenate of the sample with a labeled anti-phosphotyrosine antibody to detect the extent to which the labeled antibody becomes bound to a fragment that is about 55kDa in size as a result thereof; whereby if such about 55kDa sized fragment is not thereby detected such a result is indicative of kidney transplant rejection of claim 19. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons as set forth in the Office action mailed on 12/03/2007.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

On pages 8-12, the specification discloses:

1.) Rat kidney homogenates were subjected to a series of 30, 50, and 100 kd cut-off filters and SDS-PAGE 2- dimensional gel electrophoresis before being transferred to a membrane and immunoblotted with antiphosphotyrosine antibody. A phosphorylated protein band excised from the gel was analyzed by mass spectrometry and determined to contain phosphorylated selenium-binding protein;

2.) Baboon kidneys homogenates were subjected to two-dimensional electrophoresis (IEF and SDS-PAGE) and the gels were then either stained with Coomassie blue or silver staining or transferred to PVDF membranes and with anti- phosphotyrosine antibodies;

3.) Rhesus monkey tissue lysates were subjected to 2-D electrophoresis, transferred to a membrane and immunoblotted with anti-phosphotyrosine antibodies. A phosphorylated fifty kDa protein band was identified by mass spectrometry as containing phosphorylated SBP- **1;**

4.) Rhesus kidney lysates were subjected to a series of 100 and 50 kDa cut-off filters, 2-D electrophoresis and Western transfer before the proteins immunoblotted were with anti-SBP-I Ab. The anti-SBP-1 antibody was then stripped off and the membranes were re-immunoblotted with anti- phosphotyrosine antibody which detected identical spots; and

5.) Rhesus monkey kidney tissue samples were subjected to 2-D gel electrophoresis before being transferred to a membrane and immunolabeled with anti-SBP-1 antibodies.

The specification has disclosed a series of experiments whereby kidney homogenates are filtered, separated by gel electrophoresis and immunoblotted with anti-phosphotyrosine antibody to reveal bands, particularly one around 55kDa, which were determined by mass spectrometry or immunoblotting with anti-SBP-1 to contain phosphorylated SBP-1 or fragments thereof. The

specification also discloses a method whereby SBP-1 (SEQ ID NO: 1) is detected after electrophoresis using anti-SBP-1 antibody. However, the recited claims encompass determining the rejection status of an animal by detecting the presence of phosphorylated SBP-1 using anti-phosphotyrosine antibodies alone, though the method is not enabled for determining the presence of phosphorylated SBP-1 using only anti-phosphotyrosine antibody as anti-phosphotyrosine antibody is not specific for SBP-1 (SEQ ID NO: 1). The specification does not adequately disclose the genus of using any "labeled antibody capable of binding to the marker protein" to detect phosphorylated SBP-1 for use in the claimed method. Rather, immunoblotting a gel or a membrane with anti-phosphotyrosine antibodies will result in the visualization of any and all proteins that are phosphorylated at a tyrosine. Therefore, because of the unpredictability of the identity of the protein detected, the recited method does not accurately predict the presence of phosphorylated SBP-1 on a gel that is immunoblotted using anti-phosphotyrosine antibodies alone.

There is no way to accurately predict the identity of a protein of any given size on a gel unless the protein is analyzed to determine its specific sequence identity by a protein-specific antibody or other methods known in the art. Even if the identity of all proteins of an actual given molecular size are known, which is not the case, the identity of all proteins and protein fragments that by a given method or under a specific set of cellular conditions are visualized on a gel as a given size is not known. Protein and protein fragment sizes vary by animal species, cellular modifications and events, gel filtration conditions and as the specification acknowledges on page 4, lines 11-14, homogenation conditions. Therefore, there is unpredictability in determining the identity of proteins and fragments based upon size determined on a gel or other

laboratory procedure without confirmation of the specific identity of the protein by methods known in the art, even if all proteins of a given molecular weight were known. However, all proteins of any given molecular weight are not known, so the accuracy of the method is further reduced by the very likely possibility of detecting other proteins of the same molecular size. In particular, the art of Laminski et al. (PTO-892 mailed on 06/27/2008; Reference U) teaches that samples of baboon kidney transplants probed with anti-phosphotyrosine antibodies showed bands at *45, 55* and 66 kDa that were intensified in the presence of cAMP (In particular, page 1093, last paragraph, whole document). The Laminski reference goes on to teach that the band at 55kDa has a molecular mass that is similar to that reported for type II cyclic AMP-dependent protein kinase regulatory subunit (In particular, page 1094, last paragraph). In addition, Wade et al. (PTO-892 mailed on 06/27/2008; Reference V) teaches that UT-A2 is a 55kDa urea transporter protein found in kidneys whose expression is regulated by vasopressin (In particular, abstract, whole document) and Gang et al. (PTO-892 mailed on 06/27/2008; Reference W) teaches that osteopontin is a phosphorylated protein of 55kDa found in the kidneys and urine (In particular, abstract, first 3 paragraphs on page 374). The art of Biber et al. (PTO-892 mailed on 06/27/2008; Reference X) compared to the art of Laminski et al. (PTO-892 mailed on 06/27/2008; Reference U) shows that the experimental procedures and animal tissues used make a difference in the outcome of the results. Biber et al. teaches that rat kidneys samples probed with anti- phosphotyrosine antibodies showed bands at 40, 46 and 55 kDa that were intensified in the presence of cAMP (In particular, page 1093, last paragraph, whole document), whereas Laminski et al. teaches that samples of baboon kidneys transplants probed with anti-phosphotyrosine antibodies showed bands at 45, 55 and 66 kDa that were intensified in the

presence of cAMP (In particular, page 1093, last paragraph, whole document). Therefore, detection of a protein band of a specific molecular weight in all animals using any procedure will not generate consistent results. Because of the lack of guidance in the specification and examples and state of the art, the recited method does not accurately predict the presence of phosphorylated SBP-1 on a gel that is immunoblotted using anti-phosphotyrosine antibodies alone.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments filed on 09/29/2008 have been fully considered, but are not found persuasive.

Applicant argues:

> "The only remaining rejections relate to scope of enablement. The Office Action points out areas that are fully enabled, but expressed concerns regarding the fragment homogenate methods if only antiphosphotyrosine antibody is used for binding. In response, new claims 18 and 19 now replace all previously pending claims.
>
> New claim 18 is limited to methods relying on the full marker protein (rather than fragments from a homogenate). The Office Action is believed to indicate that at least this subject matter was fully enabled. Also, to further facilitate matters claims 18 and 19 are limited to human kidneys (with claims 2 and 9 therefore being cancelled to avoid duplication).
>
> New claim 19 focuses on the homogenate/detectable fragments/antiphosphotyrosine antibodies. While a 55kDa limitation is included without requiring a second antibody to check visualized fragments,

the Office Action's concerns regarding potential theoretical interference from other 55kDa phosphorylated proteins that the Office has now cited have been addressed in a different manner.

In this regard, the claim 19 method is now limited to when no such fragments are detected. When no such fragment is detected, it can only mean that rejection has occurred.

Normal kidney homogenate has some 55kDa. When none is found, there can have been no problematic masking interference by other phosphorylated proteins. Of course, even if Applicant had tried to use language about use of a second antibody to check out the nature of a visualized band, if no band is found there would be nothing to check out, and the inclusion of the second antibody language would not add anything.

Applicant notes that on page 10 of the Office Action the Office Action itself implied significantly less concern about enablement when there was a lack of a band at about 55kDa, than when one was evaluating decreases in intensity. Claim 19 is consistent with this approach.

Of course, even if claim 19 had not been limited to situations where no band was visualized at about 55kDa using the antiphosphotyrosine on the homogenate, it is respectfully noted that such a claim would still have been enabled. As previously noted, the submitted declaration confirms no material interference in practice (e.g. presumably because these other proteins are not present in significant amounts, or don't survive the homogenation, or are affected similarly in the standard, or are not materially upregulated when the key protein is downregulated).

The state of the record indicates that whatever theoretical concerns the Office has about such interference (regardless of how many other 55kDa phosphorylated proteins may exist in natural kidney) don't cause a practical problem. That evidence is uncontested. In any event, that argument is now moot as claim 19 now only covers situations where there is a lack of a band."

It remains the Examiner's position that the claims as recited are not enabled because they encompass the use of an anti- phosphotyrosine antibody to specifically detect phosphorylated SBP-1 and fragments thereof, as stated in the Office Action mailed on 06/27/2008. It appears that Applicants believe that the Examiner has enabled them for the detection of SEQ ID NO:1 using anti-phosphotyrosine antibody alone. This is not the case. The Examiner has enabled Applicant for specifically detecting SEQ ID NO:1 with an antibody to SEQ ID NO:1. The Examiner has enabled Applicant for detecting SEQ ID NO:1 with phosphorylated tyrosines with an antibody to SEQ ID NO:1 **and** an anti-phosphotyrosine antibody. The specification is directed to supporting the contention that anti-phosphotyrosine alone can be used to specifically detect phosphorylated SBP-1. However, it is the Examiner's position that anti-phosphotyrosine

alone cannot be used to specifically detect phosphorylated SBP-1. Therefore, the specification does not adequately disclose the genus of using any "labeled antibody that specifically binds to said marker protein" for use in the claimed method.

It is also the Examiner's position that they have provided evidence in the Office Action mailed on 06/27/2008 of the significant presence of phosphorylated proteins of 55kDa in homogenized kidney samples and particularly in transplanted baboon kidney samples. Therefore, the Applicant should be seeing those phosphorylated non-SBP-1 proteins in their experiments. As stated in the Office Action mailed on 06/27/2008, the Examiner was not concerned with the possibility of false positives which are absolute results exhibiting no phosphorylated band at 55 kDa, if that result is confirmed to be accurate. However, the Examiner is not persuaded that kidney homogenates exhibit no band at "about 55 kDa" when they are experiencing transplant rejection because those kidney homogenates should show at least the other phosphorylated proteins the Examiner has provided evidence for that are about 55 kDa.

Even if Applicants are able to perform the claimed method commensurate in scope with the claims, the method is still highly unpredictable and most likely relies on other crucial experimental factors that are not being claimed. Therefore, one of ordinary skill in the art would not be able to perform the claimed method commensurate in scope with the claims.

Applicant is encouraged to submit experimental data that is commensurate in scope with the claims to support this contention. As recited, the claimed invention is not setting forth an invention with the type of scientific rigor that is ordinary in the art. Peer-reviewed scientific

journals do not set forth experiments to specifically identify proteins using non-specific antibodies. Therefore, the Examiner is having a very difficult time being persuaded that in this case it can be done. Applicant is also encouraged to submit peer-reviewed publications that set forth experiments to specifically identify proteins from tissue samples and homogenates thereof using only anti-phosphotyrosine antibodies.

Because of the unpredictability in the method discussed *supra,* one of ordinary skill in the art would be required to perform undue experimentation to practice the claimed invention commensurate in scope with the claims.

7. No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

December 12, 2008

Nora M. Rooney

Patent Examiner

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/Maher M. Haddad/
Primary Examiner,
Art Unit 1644